

## **II. REMARKS**

Claims 1 to 75 are pending. Claims 18, 30, 58 and 67 have been withdrawn from consideration.

### **A. Regarding the Amendments**

The specification has been amended to correct a typographical error, wherein the nucleotide position "4290" inadvertently was referred to a position "4209". The amendment is supported, for example, at page 103, Table 1, where it is indicated that primer BPR19 (SEQ ID NO:4 corresponds at its 5' position to position 4290. As such, the amendment merely corrects a typographical error, and does not add new matter.

Similarly to the amendment to the specification, claims 5, 7, 12, and 65 have been amended to correct a typographical error, wherein the nucleotide position "4290" inadvertently was referred to a position "4209". The amendment is supported for the reasons discussed above.

Claim 1 has been amended to clarify that the 5' region of a primer comprises at least ten contiguous nucleotides. The amendment is supported, for example, by original claim 2 and at page 20, paragraph 41. Correspondingly, claim 2 has been amended to delete the language incorporated into claim 1.

Claims 1, 63, 65 and 66 have been amended to clarify that "PKD1" refers to the "polycystic kidney disease-associated protein -1" gene. The amendment is supported, for example, at paragraph 34, bridging pages 16-17.

Claims 7, 12 and 65 have been amended to clarify that the recited primers "selectively hybridize to SEQ ID NO:1" and can amplify a portion of SEQ ID NO:1. The amendment is supported, for example, at page 5, paragraph 12, and, therefore, does not add new matter.

Claims 20 and 66 have been amended to delete the term "about" in the phrase "at least about". The amendment merely clarifies the claimed subject matter, and does not add new matter.

**B. Regarding the Election/Restrictions**

Applicants acknowledge that the election was with respect to "a position corresponding to nucleotide 3336, wherein nucleotide 3336 is deleted", as indicated by the Examiner (see, also, page 15, paragraph 31).

Applicants further acknowledge the withdrawal of the non-elected subject matter, and the Examiner's agreement to reconsider rejoinder of the non-elected subject matter at the time of allowance, if warranted.

**C. Regarding the Claim Interpretations**

It is stated in the Office Action that the claim language "5' region" will be interpreted as at least including the single most 5' nucleotide and, in the broadest sense, every nucleotide except the 3' most; the term "3' region" is interpreted similarly. As an initial matter, Applicants point out that the claims have been amended such that they require a minimum length of 11 nucleotides for a primer (i.e., at least a 10 nucleotide 5' region and at least one nucleotide in the 3' region). Notwithstanding the amendment, it is submitted that the stated interpretation of would not appear to be reasonable at least with respect to claims 1 to 19 and 68 to 71, which are directed to "primers" and "primer pairs"; to claims 25 to 61, 72 to 75, which are directed to

methods of using such primers and primer pairs for amplification reactions; and to claims 63 to 65, directed to kits. More specifically, Applicants point out that a "primer" acts as a substrate for a polymerization reaction and, therefore, has a functional property in addition to the recited structural property (see, for example, Exhibit A, "primer...(2) short oligonucleotide of defined sequence which is annealed to the DNA template to initiate the polymerase chain reaction"). By analogy, antisense molecules comprise a functional attribute in that they inhibit translation of an RNA, and are not simply oligonucleotides that are complementary to a target nucleic acid molecule. As such, it is submitted that there would not appear to be any basis for an interpretation of the claimed subject matter that would include, for example, an oligonucleotide consisting of only 2 nucleotides (i.e., one 5' region nucleotide and one 3' region nucleotide) because such an oligonucleotide would not function as a primer for a polymerase.

It is also stated that the claim language "selectively hybridize" is interpreted as being able to hybridize under any sort of stringency conditions. Applicants again submit that this interpretation would not appear to be reasonable to the extent that the "any sort of stringency conditions" contemplated by the Examiner would not result in "selective hybridization". In this respect, it is submitted that the skilled artisan would understand the term "selectively hybridize" or "selective hybridization" to mean that an oligonucleotide (e.g., a primer) can be used to identify the presence a target nucleic acid molecule when present among other "non-target" nucleic acid molecules. Further, the specification clearly discloses that:

"the term "selectively hybridize" refers to the ability of an oligonucleotide (or polynucleotide) probe to hybridize to a selected sequence, but not to a highly related nucleotide sequence. For example, a oligonucleotide of the invention selectively hybridizes to a mutant PKD1 polynucleotide, but not substantially to a corresponding sequence of SEQ ID NO:1. As such, hybridization of the oligonucleotide to SEQ ID NO:1 generally is not above background, or, if some

hybridization occurs, is at least about ten-fold less than the amount of hybridization that occurs with respect to the mutant PKD1 polynucleotide."

See page 30, paragraph 60 (see, also, paragraphs 56 and 61). Thus, while the skilled artisan would know many different reaction conditions (e.g., reaction conditions using formamide and performed at relatively lower temperatures, or conditions lacking formamide but performed at relatively higher temperature) that similarly provide selective hybridization conditions, it is submitted that it would be improper to consider the term "selective hybridization" to include "any sort of stringency conditions", including conditions that would not be considered sufficient for selective hybridization.

It also is stated that the term "about", "at least about", and "about 50", will be interpreted as an exact definition of the specified term. It is noted that the claims have been amended to delete the term "about" from the previously recited term "at least about" and, therefore, the issue is moot with respect to this term. With respect to the term "about" or "about 50", Applicants would direct the Examiner's attention to paragraph 45, where an example of the meaning of the term "about" is provided with respect to primers as including one or few additional, or lacking one or few, nucleotides at one or both ends of a primer, and further with respect to target sequences. In view of this disclosure, it is submitted that the term "about" encompasses primers and target sequences that are insubstantially different from the specifically disclosed sequences (e.g., that lack one or a few nucleotides at an end of a primer, wherein the primer nevertheless acts as substrate for a polymerization reaction and, where recited in the claims, selectively hybridizes to a requisite target nucleic acid molecule.

#### **D. Prior Art Rejections**

The rejection of claims 1 to 7, 20 to 22, 24, 31, 37 to 39, 43, 44, 46 to 49, 59, and 62 under 35 U.S.C. § 102(b) as allegedly anticipated by Klinger et al. (U.S. Pat. No. 5,654,170) is respectfully traversed.

It is stated in the Office Action that Klinger et al. describe in Figure 3B (see, also, col. 5, line 45, to col. 6, line 4) a primer having the characteristics as set forth in claim 1 of the subject application, and that the sequence shown in Figure 3B meets the requirements of claims 2 to 4. With respect to claims 5 to 7, it is stated in the Office Action that Klinger et al. state that their invention encompasses oligonucleotides of 12 to 60 nucleotides in length that can be used to discriminate between authentic PKD1 and PKD1 homologs and can be single stranded or double stranded, and labeled or modified (citing to col. 5). It is alleged that the sequence shown in Figure 3B is an example of such an oligonucleotide.

As an initial matter, it is noted that the various grounds of rejection (see above and below) generally lack specificity and, instead, appear to merely recite the claim language verbatim. For example, with respect to the rejection of claim 6, it would appear that the sequence in Figure 3B of Klinger et al. is considered to be "substantially identical" (i.e., at least 80% identical) to one of SEQ ID NOS:3 to 51 and 61 to 113. However, no specific sequence of SEQ ID NOS:3 to 51 and 61 to 113 is identified in the Office Action as being so related to the Figure 3B sequence. For example, in comparing the 29 nucleotide SEQ ID NO:3 of the subject application with the 18 nucleotide Figure 3B sequence of Klinger et al, the longest region of identity is 6 nucleotides, which is substantially less than "at least 80% identity". A similar comparison with SEQ ID NO:4 of the subject application reveals no region of identity greater than 3 nucleotides.

It is submitted that the lack of sequence identity of the claimed primers is not particularly surprising because the Figure 3B oligonucleotide of Klinger et al. is based on a sequence of a PKD1 homolog that spans into PKD1 (compare Figures 3A and 3B; first 9 nucleotides of Fig. 3B correspond to last 9 nucleotides of unmatched portion of PKD1 homolog, and last 9 nucleotides of Fig. 3B correspond to first 9 nucleotides of PKD1 and PKD1 homolog following unmatched region). As such, at best, the Figure 3B sequence of Klinger would be expected to have no more than 50% identity to a claimed primer (note: claim 1, from claim 6 depends, requires that the 3' region not selectively hybridize to a PKD1 homolog). Further in this respect, Applicants point out that the Figure 3B oligonucleotide of Klinger et al. comprises a 5' region that hybridizes to a PKD1 homolog, and a 3' region that corresponds to a PKD1 gene and, optionally, a PKD1 homolog. As such, the oligonucleotide of Klinger et al. does not meet the requirements of claim 1 or, therefore, claim 6, which depends from claim 1. Accordingly, it is respectfully requested that the rejection be removed with respect to claim 6 (and to claim 1 for these reasons and as discussed further below).

Notwithstanding the lack of specificity of the rejections (see, also, below), it is submitted that Klinger et al. do not anticipate the subject matter of claim 1 and the claims that depend therefrom. To be anticipating, a reference must place the invention in the possession of the public. "In order to accomplish this, it must be so particular and definite that from it alone, without experiment or the exertion of his own inventive skill, any person versed in the art to which it appertains could construct and use it." (see, e.g., *In re Brown* 141 U.S.P.Q.245, 249 (Fed. Cir. 1964); citation omitted). "Prior art does not anticipate a thing unless it is enabling;...." (*Du Pont v. Cetus*, 19 U.S.P.Q. 2d 1175, 1180 (Fed. Cir. 1990)).

Claims 1 to 15 and 68 to 71 are directed to "primers" and "primer pairs", and claims 16 to 19, 25 to 61, 63 to 65, and 72 to 75 are directed to compositions or kits comprising and methods

of using such primers and primer pairs. The primers of the invention (claims 1 to 6) are characterized, in part, in that they comprise a 5' region that selectively hybridizes to a PKD1 gene sequence and, optionally, a PKD1 gene homolog sequence, and a 3' region that selectively hybridizes to a PKD1 gene sequence, and does not selectively hybridize to a PKD1 homolog sequence. The primer pairs of the invention (claims 7 to 15) are characterized, in part, in that they can selectively hybridize to and amplify specifically recited portions of SEQ ID NO:1 (e.g., nucleotides 2043 to 4290). As discussed above, "primers" (and primer pairs) comprise functional nucleic acid molecules that act as a substrate for a polymerase.

The oligonucleotide in Figure 3B of Klinger et al. does not anticipate the primers of the invention because it is not a primer, and because its 3' region hybridizes specifically to a PKD1 homolog (compare, e.g., claim 1, which requires that the 3' region does not selectively hybridize to a PKD1 homolog). The Figure 3B oligonucleotide of Klinger et al. is not a primer because it contains "a polymerization-blocking modification" at its 3' terminus (see Figure 3B, asterisk; see, also, col. 3, lines 4-8; and col. 13, line 36, to col. 14, lines 4). As Klinger et al. clearly point out, the Figure 3B oligonucleotide "is designed to hybridize specifically to the homologue sequence...this oligonucleotide...selectively prevents the amplification of PKD1 homologue sequences." (col. 6, lines 60-66; emphasis added). Thus, unlike a primer of the invention, which includes a 3' region that does not selectively hybridize to a PKD1 homolog, the oligonucleotide set forth in Figure 3B of Klinger et al. hybridizes specifically to a PKD1 homolog and is modified such that it cannot act as a substrate for a polymerase. As such, the Figure 3B oligonucleotide of Klinger et al. would appear to be irrelevant to the claimed invention and, in fact, teaches away from the primers of the invention and, consequently, compositions and methods encompassing the claimed primers.

It is noted that Klinger et al. generally refer to "isolated oligonucleotides that hybridize to the authentic expressed PKD1 gene, and not to PKD1 homologues" (see Abstract; see, also, col. 4, lines 57-60). However, Klinger et al. do not provide any specific examples of such oligonucleotides and, except for the comparison in Figure 3A, which describes a 29 nucleotide sequence present in a homolog, but not PKD1, and a single nucleotide change (see, also, col. 2, line 65, to col. 3, line 4), do not appear to provide any specific examples of a primer that can be used to discriminate between PKD1 and a PKD1 homolog (see, e.g., col. 8, lines 46-60, stating "A detailed comparison of the sequences of the authentic pKD1 gene and the homologues enables the design of primers that discriminate between authentic PKD1 gene or cDNA and homologs."). Further, except for the portion shown in Figure 3A, Klinger et al. do not appear to provide a PKD1 homolog with which a comparison can be made to identify oligonucleotides that can discriminate between PKD1 and a homolog. As such, it is submitted that Klinger et al. do not anticipate the claimed primers because the reference does not provide any examples of such primers and does not enable one skilled in the art to make such primers without a contribution of inventive skill by the artisan.

With respect to claim 7, directed to primer pairs (and claims 8 to 11, which depend from claim 7) and claim 12, which is directed to a plurality of primer pairs essentially comprising the primer pairs of claim 7, Applicants point out that Klinger et al. do not teach or suggest primer pairs that amplify the specified portions of SEQ ID NO:1. It is submitted that the "general" reference in Klinger et al. that primers can be designed to amplify portions of PKD1 does not place the claimed primer pairs in the possession of the public because there is nothing the reference that would lead one to the claimed primer pairs, which amplify only specific portions of PKD1. As such, the Klinger et al. reference merely provides a vague reference to oligonucleotides, but does not anticipate the claimed primer pairs.

With respect to claims 20, 59 and 62, it is stated that Klinger et al. teach [the language of claim 20] wherein the contiguous nucleotide sequence comprises a position corresponding to nucleotide 3336, wherein nucleotide 3336 is deleted (i.e., the elected species), and further teaches that deletions may be detected by PCR (col. 8, lines 36-40). Applicants point out that claim 59 depends from claim 44, which, in turn, depends from claim 7 (directed to primer pairs). For the reasons set forth above, it is submitted that the primer pairs of claim 7 are not anticipated by Klinger et al. and, therefore, that a method of using such primer pairs as set forth in claim 59 similarly cannot be anticipated. Further, there is nothing in Klinger et al. that teaches or suggests such a specific deletion and, therefore, the reference does not anticipate that claims for this reason, also.

With respect to claim 20 and to claim 62, which depends from claim 20, it is again submitted that there is no specificity in the rejection, only a recitation of the claim language, and no clear basis for the rejection. For example, the Office Action does not indicate where Klinger et al. describe a polynucleotide as set forth in SEQ ID NO:1 of the subject application and containing one of specified nucleotide substitutions, deletions, or insertion (e.g., a deletion of the nucleotide corresponding to position 3336 of SEQ ID NO:1). Applicants submit that the disclosure of the PKD1 sequence in Klinger et al. and a general statement in the reference stating that "deletions may be detected" does not place the presently claimed invention in possession of the public and, therefore, that the reference does not constitute an anticipatory reference with respect to the specific variant PKD1 polynucleotides set forth in claim 20. Accordingly, since Klinger et al. do not appear to refer specifically to any of the claimed polynucleotides, and absent objective evidence to the contrary, it is submitted that Klinger et al. do not anticipate claims 20 and 62.

With respect to claims 21 and 22, it is stated in the Office Action that Klinger et al. also describe including such polynucleotides in a vector or host cell (citing to cols. 6-7). Applicants point out, however, that claims 21 and 22, depend from claim 20, and, for the reasons discussed above, Klinger et al. do not appear to describe the polynucleotides of claim 20. As such, absent clarification of the rejection of claim 20 and objective evidence that Klinger et al. describe the polynucleotides of claim 20, it is submitted that the reference does not anticipate the subject matter of claims 21 and 22.

With respect to claims 25 and 43, it is stated in the Office Action that Klinger et al. describe "a method of detecting the presence or absence of a mutation in a PKD1 polynucleotide [using] at least one primer pair of claim 7". Applicants submit, however, for the reason set forth above, Klinger et al. do not teach or suggest primer pairs as set forth in claim 7 and, therefore, cannot anticipate a method of using such primer pairs as set forth in claim 25. Also, although it is stated that claim 43 is included in this rejection, only the language of claim 25 is recited in the rejection. As such, there does not appear to be any rejection of claim 43. Nevertheless, Applicants point out that claim 43 depends from claim 20 and, therefore, for the reasons set forth above with respect to claim 20, it is submitted that Klinger et al. do not anticipate the subject matter of claim 43.

With respect to claim 31, it is stated in the Office Action that Klinger et al. describe determining the nucleotide sequence of the amplification product (col. 8, lines 35-38). Applicants point out, however, that, at the cited passage, Klinger et al. refer to detecting PKD1 mutations in different ways, including sequencing the PKD1 gene, or using PCR and determining the sizes of the fragments. Klinger et al. do not teach or suggest sequencing PCR amplification products. Nevertheless, Applicants point out that claims 31 depends from claim 25, which, in turn, depends from claim 7, directed to primer pairs. For the reasons set forth above, it is

submitted that the primer pairs of claim 7 are not anticipated by Klinger et al. and, therefore, that a method of using such primer pairs as set forth in claim 31 similarly cannot be anticipated.

With respect to claims 37, 44 and 49, it is stated in the Office Action that Klinger et al. describe detecting a mutation by a primer extension assay using a labeled primer (col. 5, line 52) and a mixture of deoxy-and dideoxy-nucleotides (col. 14, lines 1-10), and describe testing samples from a subject (cols. 13-14). It is noted that claim 49 is included in this rejection, but that there does not appear to be a basis for the rejection of claim 49. Nevertheless, Applicants point out that claim 49 depends from claim 44, which, in turn, depends from claim 7, directed to primer pairs. For the reasons set forth above, it is submitted that the primer pairs of claim 7 are not anticipated by Klinger et al. and, therefore, that a method of using such primer pairs as set forth in claim 49 similarly cannot be anticipated. If the rejection of claim 49 is maintained, clarification of the basis of the rejection is respectfully requested.

With respect to claims 37 and 44, Applicants point out that claim 37 depends from claim 25, which, in turn, depends from claim 7, and that claim 44 similarly depends from claim 7, directed to primer pairs. For the reasons set forth above, it is submitted that the primer pairs of claim 7 are not anticipated by Klinger et al. and, therefore, that a method of using such primer pairs as set forth in claims 37 and 44 similarly cannot be anticipated.

With respect to claims 38, 39 and 48, it is stated in the Office Action that Klinger et al. describe the method of claims 37 and 44 using a plurality of primers and in a high throughput format (citing to col. 11, lines 11-17). Applicants point out, however, that claims 37 and 44 ultimately depend from claim 7 and, as discussed above, Klinger et al. do not teach or suggest the primer pairs of claim 7. As such, the reference cannot anticipate the methods of claim 38, 39, and 48, which require the primer pairs of claim 7.

With respect to claims 46 and 47, it is stated in the Office Action that Klinger et al. describe that identifying the presence or absence of a mutation is indicative of a PKD1 associated disorder (col. 1, lines 10-49). Applicants point out, however, that claims 46 and 47 depend from claim 44, which, in turn, depends from claim 7. As discussed above, Klinger et al. do not teach or suggest the primer pairs of claim 7 and, therefore, the reference cannot anticipate the methods of claim 46 and 47, which require the primer pairs of claim 7.

In summary, Klinger et al. do not teach or suggest the claimed primers or primer pairs and, therefore, cannot teach or suggest compositions that comprise the primers or primer pairs or methods of using them. As such, it is submitted that the Klinger et al. reference does not anticipate the claimed invention and, therefore, respectfully requested that the rejections of claims 1 to 7, 20 to 22, 24, 31, 37 to 39, 43, 44, 46 to 49, 59, and 62 as anticipated by Klinger et al. be removed. If any of the rejections is maintained, it is respectfully requested that the basis of the rejections be set forth with sufficient specificity.

The rejection of claims 16, 17, 19, 40 and 42 under 35 U.S.C. § 102(b) as allegedly anticipated by Brennan (U.S. Pat. No. 5,474,796) is respectfully traversed.

It is stated in the Office Action that Brennan describes an array having thereon every possible 10-mer nucleic acid, which, it is alleged, inherently comprises all of the plurality of primer sequences capable of hybridizing to PKD1. With respect to claims 16, 17, and 19, Applicants point out that amended claim 1, from which the rejected claims ultimately depend, require that a primer of the invention is at least 11 nucleotides in length (i.e., a 5' region comprising at least ten contiguous nucleotides, and a 3' region, which must comprise at least one nucleotide). Brennan does not teach or suggest at least 11-mers, or arrays comprising at least 11-mers and, therefore, does not anticipate the subject matter of claim 16, 17 and 19.

With respect to claims 40 and 42, Applicants point out that the claims require that the "plurality of samples" are in an array, not the primer pairs (see claim 25, from which claims 40 and 42 ultimately depend). Brennan does not teach or suggest a plurality of samples in an array and, further, does not teach or suggest "primer pairs". As such, the reference cannot teach the method of claim 25 or of claims 40 and 42, which depend therefrom. Accordingly, it is respectfully requested that the rejection of claims 16, 17, 19, 40 and 42 as anticipated by Brennan

The rejection of claims 8 to 15, 26, 28, 29, 54, 68 to 72 and 74 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Buck et al. is respectfully traversed.

Klinger et al. is applied as discussed above. It is stated in the Office Action that Klinger et al. do not teach the primers set forth as SEQ ID NOS:3, 4, 19 and 20, only the sequence in the genomic form of SEQ ID NO:1 (referring to "alignments"). It is stated that it would have been obvious to one of ordinary skill in the art to select the primers set forth as SEQ ID NOS:3, 4, 19, and 20 from the PKD1 sequence of Klinger et al. "for the expected benefit of obtaining functionally equivalent primers with the ability to "selectively prevent the amplification of PKD1 homologue sequences. In this manner authentic PKD1 sequences are selectively amplified (Col. 5 lines 64-67)." (see Office Action, paragraph bridging pages 12-13). In support of the rejection, it is stated that Buck teaches that any of various different primers are functionally equivalent and, citing to *In re Deuel*, which states that "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties...", alleged that the claimed primers merely represent structural homologs that can be derived from the sequences suggested by the prior art as useful for detecting PKD1, but not PKD1 homologs.

Applicants note that alignments were not received with the present Office Action. Nevertheless, Applicants point out that each of the rejected claims ultimately depend from

claim 7 (or from claim 12, which essentially provides a plurality of the primer pairs of claim 7) and, as discussed above, Klinger et al. merely provides a vague description of oligonucleotides that one may be able to identify, but do not teach or suggest with any specificity the primer pairs of claim 7 (or claim 12). Thus, Klinger et al. do not provide any "known compounds" or, therefore, any "Structural relationships [that] may provide the motivation or suggestion [ ] to obtain new compounds." Buck similarly does not describe with any specificity oligonucleotides useful as primer pairs for amplifying the specified portions of PKD1 as recited in the claims and, therefore, does not provide the teaching that is missing from Klinger et al.

In summary, the combination of a general teaching of primers by Klinger et al. with a teaching that every primer was equally effective in amplifying a particular polynucleotide would not have provided one of ordinary skill in the art with a reasonable expectation of obtaining the claimed primer pairs, which amplify the specified portions of PKD1 as recited in the claims. Accordingly, it is respectfully requested that the rejection of claims 8 to 15, 26, 28, 29, 54, 68 to 72 and 74 as unpatentable over Klinger et al. in view of Buck et al. be removed.

The rejection of claims 27, 53, 55, 60, 61, 73 and 75 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Buck et al., and further in view of Shapira et al. is respectfully traversed.

Klinger et al. and Buck et al. are applied as discussed above. It is stated in the Office Action that Klinger et al. and Buck et al. do not describe the nesting of primers, but that Shapira et al. describe amplifying nucleic acids using nested PCR. As such, it is alleged that it would have been obvious to combine the cited references to obtain the benefits provided by nested PCR.

Applicants point out that claims 27, 53, 55, 60, 61, 73 and 75 ultimately depend from claim 7. For the reasons set forth above, it is submitted that Klinger et al. and Buck et al., either alone or in combination, do not teach or suggest the primer pairs of claim 7 and, therefore, do not

teach or suggest methods of using the primer pairs. Shapira et al. do not teach or suggest primer pairs that can amplify the portions of PKD1 as recited in claim 7 and, therefore, do not provide the teaching that is missing in Klinger et al. and Buck et al. Accordingly, it is respectfully requested that the rejection of claims 27, 53, 55, 60, 61, 73 and 75 as unpatentable over Klinger et al. in view of Buck et al., and further in view of Shapira et al. be removed.

The rejection of claims 32, 33, 35 and 36 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Buck et al., and further in view of Sathe et al. is respectfully traversed.

Klinger et al. and Buck et al. are applied as discussed above. It is stated in the Office Action that Klinger et al. and Buck et al. do not describe using temperature melting HPLC or SSCP analysis on an amplification product to detect a mutation, but that Sathe et al. describe detecting mutations using such methods. As such, it is alleged that it would have been obvious to combine the cited references to obtain the benefits of the techniques of Sathe et al. as a viable alternative to direct sequencing to detect mutation.

Applicants point out that claims 32, 33, 35 and 36 ultimately depend from claim 7. For the reasons set forth above, it is submitted that Klinger et al. and Buck et al., either alone or in combination, do not teach or suggest the primer pairs of claim 7 and, therefore, do not teach or suggest methods of using the primer pairs. Sathe et al. do not teach or suggest primer pairs that can amplify the portions of PKD1 as recited in claim 7 and, therefore, do not provide the teaching that is missing in Klinger et al. and Buck et al. Accordingly, it is respectfully requested that the rejection of claims 32, 33, 35 and 36 as unpatentable over Klinger et al. in view of Buck et al., and further in view of Sathe et al. be removed.

The rejection of claims 16, 17, 19, 40 and 42 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Brennan is respectfully traversed.

Klinger et al and Brennan are applied as discussed above. It is stated in the Office Action that Klinger et al. do not teach the immobilization of primers on a solid matrix, but that Brennan describes an array containing every possible 10-mer. As such, it is alleged it would have been obvious to combine Klinger et al. with Brennan to obtain the benefit of producing dense arrays in a reproducible manner.

Applicants first point out that the claims are not directed to methods of producing arrays and, therefore, that the "benefit of producing dense arrays" provided by Brennan would not appear to be particularly relevant to the claimed subject matter. As such, it would not appear that, absent hindsight analysis, one of ordinary skill in the art would have been motivated to combine Brennan with Klinger et al. because there is nothing in Klinger et al. to suggest arrays and nothing in Brennan to suggest PKD1.

Notwithstanding the above, Applicants also point out that claims 16, 17, 19, 40 and 42 were rejected as anticipated by Brennan. As discussed above with respect to the novelty rejection, claims 40 and 42, which depend from claim 39, are directed to a "plurality of samples" in an array, not primers. As such, Brennan et al. is irrelevant to claims 40 and 42, and Klinger et al. do not teach or suggest such a plurality of samples. As such, it is submitted that the cited references, either alone or in combination, would not have made the subject matter of claims 40 and 42 obvious.

With respect to claims 16, 17, and 19, it is noted that these claims ultimately depend from amended claim 1, directed to primers that are at least 11 nucleotides in length. Brennan does not teach or suggest at least 11-mers, or arrays comprising at least 11-mers, and Klinger et al. do not teach or suggest arrays of primer or, as discussed above, primers as set forth in amended claim 1. As such, the references, either alone or in combination, would not have made the subject matter of claims 16, 17 and 19 obvious. Accordingly, it is respectfully requested that the rejections of claims 16, 17, 19, 40 and 42 as unpatentable over Klinger et al. in view of Brennan be removed.

The rejection of claim 41 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Brennan is respectfully traversed.

Klinger et al. and Brennan are applied as above. It is stated that the reference (i.e., Klinger et al.) does not teach that the primers can be immobilized on a solid matrix such as a microtiter plate, but that Brennan teaches an array of wells such as in a microtiter plate. As such, it is alleged that it would have been obvious to combine the references to obtain the subject matter of claim 41 for the benefit of producing large, dense arrays in a reproducible manner.

Applicants point out, however, that the "array" referred to in claim 41 is an array of "a plurality of samples", not primers. Neither Klinger et al. nor Brennan teaches or suggest a plurality of samples in an array and, therefore, would not have made the claimed subject matter obvious. Accordingly, it is respectfully requested that the rejection of claim 41 as unpatentable over Klinger et al. in view of Brennan be removed.

The rejection of claims 50 to 52 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Iliff is respectfully traversed.

Klinger et al. is applied as discussed above. It is stated that Klinger et al. do not teach or suggest transmitting a report via internet fax, or mail, but that Iliff describes a disease management system that provides such options to patients as a means of receiving information such as a summary of a consultation session. It is stated that it would have been obvious to combine the teachings of the cited references for the expected benefit of promoting patient health in a cost effective manner.

Applicants point out that claims 50 to 52 ultimately depend from claim 7. For the reasons set forth above, it is submitted that Klinger et al. do not teach or suggest the primer pairs of claim 7 and, therefore, do not teach or suggest methods of using the primer pairs as required of claims 50 to 52. Iliff et al. do not teach or suggest primer pairs that can amplify the portions of PKD1 as recited in claim 7 and, therefore, do not provide the teaching that is missing in Klinger

et al. Accordingly, it is submitted that the cited references, either alone or in combination, would not have rendered the claimed subject matter obvious and, therefore, respectfully requested that the rejection of claims 50 to 52 as unpatentable over Klinger et al. in view of Iliff be removed.

The rejection of claims 55 to 57 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Buck et al., and further in view of Shapira et al. and of Sathe et al. is respectfully traversed.

Klinger et al., Buck et al., and Shapira et al. are applied as discussed above. It is stated in the Office Action that Klinger et al., Buck et al., and Shapira et al. do not describe using temperature melting HPLC or SSCP analysis on an amplification product to detect a mutation, but that Sathe et al. describe detecting mutations using such methods. As such, it is alleged that it would have been obvious to combine the cited references to obtain the benefits of the techniques of Sathe et al. as a viable alternative to direct sequencing for mutation detection.

Applicants point out that claims 55 to 57 ultimately depend from claim 7. For the reasons set forth above, it is submitted that Klinger et al., Buck et al., and Shapira et al., either alone or in combination, do not teach or suggest the primer pairs of claim 7 and, therefore, do not teach or suggest methods of using the primer pairs. Sathe et al. also do not teach or suggest primer pairs that can amplify the portions of PKD1 as recited in claim 7 and, therefore, do not provide the teaching that is missing in Klinger et al., Buck et al., and Shapira et al. Accordingly, it is submitted that the cited references, either alone or in combination, would not have rendered the claimed subject matter obvious and, therefore, respectfully requested that the rejection of claims 55 to 57 as unpatentable over Klinger et al. in view of Buck et al., and further in view of Shapira et al. and of Sathe et al. be removed.

The rejection of claims 63 to 66 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Ahern et al. is respectfully traversed.

Klinger et al. is applied as discussed above. It is stated in the Office Action that Klinger et al. do not describe a kit for detecting the presence or absence of a mutation in PKD1, but that Ahern et al. teach that kits offer scientists a good return on investment by providing required reagents. As such, it is alleged that it would have been obvious to combine the cited references for the benefit of convenience and to save time.

The kits of claims 63 and 64 contain primers, which are defined the same as the primers of claim 1. The kits of claim 65 contain primer pairs, which are defined the same as the primer pairs of claim 7. The kits of claim 66 contain polynucleotides, which are defined the same as the polynucleotides of claim 20. For the reasons set forth above, Klinger et al. do not describe such primers, primer pairs, or polynucleotides. Ahern et al. similarly do not teach or suggest such primers, primer pairs, or polynucleotides and, therefore, do not provide the teaching that is missing in Klinger et al. Accordingly it is submitted that the cited references, either alone or in combination, would not have rendered the claimed kits obvious and, therefore, respectfully requested that the rejection of claims 63 to 66 as unpatentable over Klinger et al. in view of Ahern et al. be removed.

The rejection of claim 34 under 35 U.S.C. § 103(a) as allegedly unpatentable over Klinger et al. in view of Buck et al., and further in view of Koster et al. is respectfully traversed.

Klinger et al. and Buck et al. are applied as discussed above. It is stated in the Office Action that Klinger et al. and Buck et al. do not describe the use of MALDI-TOF mass spectrometry to detect the presence or absence of a mutation in an amplification product, but that Koster et al. teach that MALDI-TOF can be used to sequence nucleic acids by analysis of nested fragments. As such, it is alleged that it would have been obvious to combine the cited references for the benefit of obtaining a high speed, high throughput method.

Applicants point out that each of the rejected claims ultimately depend from claim 7 and, as discussed above, Klinger et al. merely provides a vague description of oligonucleotides that

one may be able to identify, but do not teach or suggest with any specificity the primer pairs of claim 7, particularly not the primer pairs set forth as SEQ ID NOS:3 and 4 and SEQ ID NOS:19 and 20, and that Buck similarly does not describe with any specificity oligonucleotides useful as primer pairs for amplifying the specified portions of PKD1 as recited in the claims. Koster et al. also do not teach or suggest such primers or primer pairs and, therefore, do not provide the teaching missing in Klinger et al. and Buck et al. Accordingly, it is submitted that the cited references, either alone or in combination, would not have rendered the claimed subject matter obvious and, therefore, respectfully requested that the rejection of claim 34 as unpatentable over Klinger et al. in view of Buck et al., and further in view of Koster et al. be removed.

**E. Rejections under 35 U.S.C. § 112**

The rejection of claims 1 to 17, 19 to 57, 59 to 66, and 68 to 75 under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out the subject matter regarded as the invention is respectfully traversed.

It is stated in the Office Action that the recitation of the term "PKD1" is unclear. The claims have been amended to clarify that the term refers to "polycystic kidney disease-associated protein-1". As such, it is requested that this rejection be removed.

It is also stated that the term "at least about" is unclear because it is unclear as to the extent of variance allowed by the term "about". The claims have been amended such that the term "about" has been deleted in reference to the term "at least." As such, it is requested that this rejection be removed.

In view of the amendments, it is submitted that the claims clearly define the subject matter regarded as the invention. Accordingly, it is respectfully requested that the rejection of claims 1 to 17, 19 to 57, 59 to 66, and 68 to 75 under 35 U.S.C. § 112, second paragraph, be removed.

The objection to the specification and corresponding rejection of claims 1 to 66 and 68 to 75 under 35 U.S.C. § 112, first paragraph, as allegedly lacking a written description are respectfully traversed.

It is stated that the claims encompass a variety of primers, primer pairs, and polynucleotides, but that claim 7 as written, for example, could encompass any T3 or T7 primer pair that "can amplify" a cloned region of SEQ ID NO:1 comprising about nucleotides 2043 to 4290. It is stated that "the instant claims encompass nucleic acids and methods that comprise any number of potential sequences when one considers that they encompass nucleic acids that comprise partial matches to the recited SEQ ID numbers and the ability to 'hybridize' to and 'can amplify' even more sequences." (OA, page 23, first paragraph). As such, it is alleged that the claims encompass any number of possible primers comprising any number of known and unknown nucleic acid fragments, but that the specification only discloses SEQ ID NO:1 and primers of SEQ ID NOS:3, 4, 19 and 20. It is further alleged that "...the sequence of nucleotides of SEQ ID NO:1 and all aforementioned variations, are essential to the operation and function of the claimed invention. None of these sequences meet the written description provision...." (*Id.*)

With respect to the specific example regarding the primer pairs of claim 7, the Examiner's point is well taken. Accordingly, claim 7, as well as claims 12 and 65, which contain similar language, have been amended to clarify that the primer pairs selectively hybridize to SEQ ID NO:1 and can amplify a portion of SEQ ID NO:1 as recited.

With respect the rejection in general, however, Applicants respectfully disagree. First, as discussed in Section II.C., above, the interpretations attributed to various terms used in the claims are not commensurate with the meaning that one skilled in the art would attribute to the terms. Further, in the present rejection, the language of the claims appears to have been read incorrectly. For example, it is stated that the claims encompasses primers comprising regions wherein "at least 10 contiguous nucleotides 'can hybridize'" (OA, page 23, first paragraph; emphasis added). Applicants point out, however, that such language (see, e.g., claim 2 prior to the present

amendment) is in a dependent claim and, therefore, must be read in the context of the independent claim from which it depends (e.g., claim 1). In this respect, claim 1 requires that the 5' region "selectively hybridizes" and, therefore, unless the limitation of "selectively hybridize" is properly read into claim 2, dependent claim 2 would improperly be broader than claim 1. With respect to the term "can amplify" (e.g., claims 7 and 12), Applicants point out that the claims have been amended to clarify that the claimed primers "selectively hybridize to SEQ ID NO:1 and can amplify a portion of SEQ ID NO:1" as recited.

Second, Applicants submit that, while SEQ ID NOS:3 and 4 provide only a single example of a primer pair that can amplify the portion of SEQ ID NO:1 comprising about nucleotide 2043 to 4290, the subject application provides seven additional examples of primer pairs (SEQ ID NOS:5 to 18), which together with SEQ ID NOS:3 and 4 prepare PKD1-specific amplification products that encompass all of the exons and their flanking introns within the replicated region of the PKD1 gene (see, e.g., page 22, paragraph 45; see, also, Figure 1, and paragraph 37 bridging pages 17-18). Further, while SEQ ID NOS:19 and 20 provide only a single example of a nested primer pair that can amplify a portion of the amplification product generated using SEQ ID NOS:3 and 4 that includes the deletion corresponding to position 3336 of SEQ ID NO:1, the subject application provides numerous examples of additional nested primer pairs (SEQ ID NOS:21 to 51 and 61 to 112), each of which allows detection of other PKD1 gene mutations (see Table 2, page 105). As such, it is submitted that the skilled artisan, upon considering the disclosure of the elected species of primer pairs (SEQ ID NOS:3, 4, 19 and 20) in view of the entire application, which provides numerous specific examples of primers and primer pairs useful for practicing the claimed methods, would have known that Applicants were in possession of the present invention. Accordingly, it is respectfully requested that the rejection of claims 1 to 66 and 68 to 75 under 35 U.S.C. § 112, first paragraph under 35 U.S.C. § 112, first paragraph, be removed.

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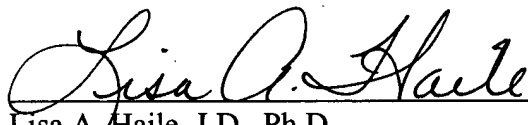
PATENT  
Attorney Docket No.: JHU1680-2

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Enclosed is Check No. 560343 in the amount of \$110.00 in payment of the one (1) month extension of time fee. The Commissioner is hereby authorized to charge any other fees that may be associated with this communication, or credit any overpayment, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: May 28, 2004

  
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Attachment: Exhibit A

RNA polymerase at the transcription start site. It is also known as the -10 site. See: BACTERIAL GENE EXPRESSION; TRANSCRIPTION.

**primaquine** An antimalarial drug used to eliminate hepatic forms of *Plasmodium vivax* and *P. ovale*. When given to individuals with GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY it may cause severe haemolysis.

**primary cell culture** Cultured cells derived directly from normal tissues rather than from tumours or from CELL LINES. Primary cultures are usually from skin or embryonic tissues and are predominantly FIBROBLASTS. Unlike cell lines, primary cell cultures will only undergo a limited number of cell divisions.

**primary immune response** The IMMUNE RESPONSE that occurs following the first exposure to an ANTIGEN. The rate of development and magnitude of this response depends upon the immunogenicity of the antigen, but it is usually slower and smaller than the response following subsequent exposure to the same antigen (the SECONDARY IMMUNE RESPONSE). In the primary response there is usually a lag period of several days between the introduction of the antigen and the appearance of specific ANTIBODY or T lymphocytes (T CELLS) in the blood. Serum antibody is of low TITRE and usually of low AFFINITY, with a relative predominance of IgM. See also: B CELL DEVELOPMENT; T CELL DEVELOPMENT.

**primary induction, primary embryonic induction** See: NEURAL INDUCTION.

**primary lysosome** Historically it was supposed that newly formed LYSOSOMES derived directly from the GOLGI APPARATUS as small vesicles of ~0.1 µm in diameter containing ACID PHOSPHATASE but no endocytosed material, and which were thus called primary lysosomes. The model largely derived from the observation in neutrophils of azurophilic granules which can fuse with phagosomes to form phagolysosomes. This model, for which the evidence has always been weak and mainly morphological, is now disputed and the origin of mature lysosomes is thought to be more complex.

**primary nondisjunction** See: NONDISJUNCTION.

**primary oocyte** See: OOGENESIS.

**primary structure** The AMINO-ACID SEQUENCE of a protein or the NUCLEOTIDE sequence of DNA or RNA.

**primary transcript** The RNA produced by TRANSCRIPTION of a gene, and which often must undergo further processing to yield a functional mRNA or other structural RNA. See: RNA PROCESSING; RNA SPLICING; RIBOSOMAL RNA.

**primase** RNA POLYMERASE that synthesizes the short RNA primers for DNA REPLICATION using DNA as a template. The enzyme in *Escherichia coli* is of  $M_r$  60 000 and synthesizes a short stretch of ~5 nucleotides.

**primed-burst paradigm** Pattern of stimulation mimicking natural hippocampal THETA RHYTHM. This pattern of stimulation (a single priming pulse followed, after about 150 ms, by a 100 Hz burst of two or more stimuli) is effective in inducing LONG-TERM POTENTIATION.

**primer** (1) In DNA REPLICATION a short stretch of RNA that is synthesized by a specialized RNA polymerase (PRIMASE) using the DNA as a template and which is then elongated by DNA polymerase. The primer is subsequently excised and the gap filled in by a DNA polymerase.

(2) Short oligonucleotide of defined sequence which is annealed to the DNA template to initiate the POLYMERASE CHAIN REACTION.

**primitive lattice, primitive unit cell** A description of particular SYMMETRY arrangements found in crystals having only one LATTICE point in each UNIT CELL. In contrast, a non-primitive cell or lattice has an additional lattice point at the centre of the unit cell or at the centres of one (or all three) pair(s) of opposite faces of the unit cell. These arrangements, which are referred to as centred lattices or centred unit cells, can be recognized by the pattern of SYSTEMATIC ABSENCES seen in the DIFFRACTION pattern from the crystal. See: X-RAY CRYSTALLOGRAPHY.

**primitive streak** A groove that forms along the longitudinal axis of the bilaminar germ disk early in the development of mammalian and avian embryos. During GASTRULATION, where the two-layer embryo becomes a three-layer disk, cells of the epiblast (primitive ECTODERM) migrate toward the midline of the germ disk where they detach from the epiblast and move beneath it, forming the invagination of the primitive streak. Some of the epiblast cells displace the cells of the underlying hypoblast (primitive ENDODERM), while others migrate between the two layers to form the MESODERM. Soon after gastrulation commences, HENSEN'S NODE, which initially lies at the end of the primitive streak, regresses caudally, laying down the notochord. See also: AVIAN DEVELOPMENT; MAMMALIAN DEVELOPMENT.

**primordial germ cells (PGC)** Small diploid precursor cells of sperm and eggs. It is possible to follow the life histories of primordial germ cells in a number of species, using their high level of alkaline phosphatase enzyme activity as a marker, and certain common features of their development have been discovered. They usually arise as a small number of cells in the posterior of the organism, such as the posterior pole of the *Drosophila* blastoderm, or at the posterior end of the vertebrate PRIMITIVE STREAK. They are highly motile and prolific. Shortly after they are first identifiable, they begin to migrate towards the developing gonads, dividing frequently as they go. Eventually, large numbers reach the gonad, become stationary, and commence MEIOSIS. It is not until they reach the developing gonads that male and female primordial germ cells become distinguishable.

**primordium** A structure or region which is the precursor of an adult structure or organ. The German word ANLAGE is often used as a synonym.

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